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Hypothesis

miR-139-5p Regulates *PIEZO1* Expression to Modulate Radiation-induced Injury in Type II Alveolar Epithelial Cells: A Hypothesis

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Abstract

Radiation-induced pulmonary injury (RIPI) is a common adverse reaction when ionizing radiation acts on the lung. Type II alveolar epithelial cells participate in the process of RIPI by regulating inflammation, epithelial-mesenchymal transition, cellular senescence, etc. The expression of miR-139-5p is inhibited by ionizing radiation, which plays a role in modulating radiotherapy resistance in breast cancer tissues. *PIEZO1*, a mechano-sensitive ion channel, has been found to play an essential role in bleomycin-induced lung fibrosis. Moreover, there exist some common mechanisms between bleomycin-induced lung fibrosis and RIPI. The stretch changes during RIPI might also regulate *PIEZO1* signaling. Furthermore, *PIEZO1* is predicted to be a downstream target gene of miR-139-5p, and ionizing radiation leads to increased *PIEZO1* mRNA and protein expression. We hypothesized that miR-139-5p might regulate *PIEZO1* expression to modulate radiation-induced injury in type II alveolar epithelial cells. Therefore, it is of great practical significance to explore new ways to prevent and treat RIPI and break through the existing research bottlenecks for improving the prevention and treatment of RIPI.

Introduction

The human lung is a sensitive organ to ionizing radiation.[1] Radiation-induced pulmonary injury (RIPI) could happen not only in radiotherapy for chest tumors, but also in practitioners receiving long-term low-dose radiation.[2] Approximately 35% of lung and breast cancer patients would develop RIPI after chest radiation therapy.[3] RIPI is mainly divided into three stages comprising the asymptomatic phase,[4] radiation-induced pneumonitis,[5] and radiation-induced lung fibrosis.[6,7] When the disease progresses to the pulmonary fibrosis, this would cause not only irreversible damage to the respiratory system and affect the long-term quality of life, but also induce life-threatening respiratory failure.[3,7] Hence, finding interventions to delay or reverse the development of RIPI remains a critical issue in current clinical practice. In particular, early therapeutic intervention could significantly improve survival in RIPI.

In addition, type II alveolar epithelial cells play an essential role in lung injury caused by ionizing radiation.[3] Extensive type II alveolar epithelial cells would be damaged after radiation stimulated the release of pro-inflammatory cytokines, thus leading to aggravated lung inflammation, increased epithelial and endothelial cell injury, and enhanced proliferation of interstitial cells and interstitial edema.[8]

PIEZO1 is a mechanically sensitive ion channel discovered in recent years.[9] It is expressed in various lung cells according to the epithelial cells (bronchus and alveolus) and endothelial cells.[10–12] A recent study has found that cyclical hydrostatic pressure could trigger an inflammatory response by activating the ion channel *PIEZO1* in myeloid cells of the lung.[13] Similarly, in the progress of RIPI, the damaged mechanical characteristics of the cellular microenvironment could also be sensed by *PIEZO1*.[14]

Keywords: Ionizing radiation; miR-139-5p; *PIEZO1*; Radiation-induced pulmonary injury.

Abbreviations: RIPI, Radiation-induced pulmonary injury; RLE-6TN, rat type II alveolar epithelial cells.

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In addition to the change in the activation status of *PIEZO1*, whether there is a change in the *PIEZO1* expression during RIPI is still unclear.

However, there are many studies confirming the relationship between miRNAs and lung injury. In an acute lung injury model, miRNA-1246 could mediate lung inflammation and apoptosis through *NF-κB* activation and *Wnt/β-catenin* inhibition.[15] One study found that miR-34b-3p, miR-96-5p, and miR-802-5p in C57BL/6 mice lung tissue were associated with TGF-β signaling after whole chest irradiation.[16]

Compared with normal bronchial epithelial cells, the miR-139-5p had a low expression in lung adenocarcinoma cells.[17] Furthermore, the expression of miR-139-5p was significantly decreased after a single 3-Gy dose of irradiation for 4–8 h in breast cancer cells. Reduced miR-139-5p expression was related to radiotherapy resistance of breast cancer cells by upregulating the target genes.[18] Several miRNAs predicting databases, such as TargetScanHuman 7.2,[19] miRBase,[20,21] and ENCORI,[22] also predicted that *PIEZO1* could be the target gene of miR-139-5p (Fig. 1a–c).[23] Nevertheless, whether the impact of miR-139-5p on radiation-induced injury in type II alveolar epithelial cells depends on *PIEZO1* signaling is still unknown.

Hypothesis

We hypothesize that during RIPI, *PIEZO1* expression is enhanced following reduced expression of miR-139-5p, which would participate in the pathogenesis of RIPI in type II alveolar epithelial cells. Firstly, *PIEZO1* would be predicted to be the target gene of miR-139-5p by some miRNAs target gene prediction resources.[19] Previous research has proven that ionizing radiation could inhibit the expression of miR-139-5p and upregulate downstream target genes related to radiotherapy resistance.[18] We thereby assume that ionizing radiation could upregulate the expression of *PIEZO1* by downregulating miR-139-5p. Secondly, it was shown that *PIEZO1* could promote *HIF-1α* accumulation in myeloid cells to regulate innate immunity and bleomycin-induced lung fibrosis.[13] Thirdly, *HIF-1α* was involved in the pathogenesis of radiation-induced pneumonia.[24] Thereby, this would seem reasonable to speculate that *PIEZO1* could also be activated and aggravate lung inflammation through *HIF-1α* when type II alveolar epithelial cells were exposed to ionizing radiation (Fig. 2).

Statistical analysis

GraphPad software 8.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used to perform the statistical analyses. Data were presented as the mean ± standard deviation (SD). Differences among groups were evaluated by a student's *t*-test. Each experiment was repeated as three independent experiments unless specified. $p < 0.05$ was considered to be statistically significant.

Rationale for the hypothesis

RIPI and miR-139-5p

miR-139-5p was initially identified as a tumor suppressor gene in breast cancer,[25] colorectal cancer,[26] prostate cancer,[27,28] and bladder cancer.[29] It was also found to be an effective regulator of the radiotherapy response.[30,31] After ionizing radiation, the expression of miR-139-5p was inhibited in breast cancer cells.[18] This led to an increased expression of the miR-139-5p target genes related to radiotherapy resistance, such as *POLQ, TOP1, TOP2A*, and *MAT2A*.[18] Conversely, miR-139-5p mimics have a strong synergistic effect with radiation *in vitro* and *in vivo*. Furthermore, miR-139-5p could modulate *Notch1* signaling, and an overexpression of miR-139-5p could downregulate the expression of the *Notch1* protein that could inhibit an epithelial-mesenchymal transition, which would be a critical process in the development of RIPI.[32] Taken together, this evidence would suggest that miR-139-5p might play a role in RIPI.

PIEZO1 might be a downstream target gene of miR-139-5p

We chose the TargetScanHuman 7.2,[19] miRBase,[20,21] and ENCORI[22] miRNA target predicting resources to search for potential miR-139-5p target genes related to RIPI. The above three databases all predicted that *PIEZO1* was possibly a target of miR-139-5p, which the intersection of the three databases predictions had 238 genes (Fig. 1d). Two of the three databases displayed a high predictive score in *PIEZO1*, a target score of 82 in miRBase and 99 context++ score percentile in TargetScanHuman 7.2. More interestingly, the impacts of miR-139-5p and *PIEZO1* expression on the survival of patients with breast cancer were contrasting.[23] It was shown that a high expression of miR-139-5p (Fig. 1e) or low expression of *PIEZO1* (Fig. 1f) was related to longer survival time in breast cancer patients. The inverse effects of miR-139-5p and *PIEZO1* on the breast cancer prognosis were consistent with the prediction that miR-139-5p negatively regulated the *PIEZO1* expression made by the miRNA target predicting databases.

PIEZO1 in type II alveolar epithelial cells

As a mechanically sensitive ion channel, *PIEZO1* would be crucial for the generation of mechanically gated non-selective cation current and would play an important role in the process of mechanical transduction.[33] Previous studies and data from the BioGPS database (http://biogps.org/) demonstrated that *PIEZO1* was widely expressed in various kinds of lung (fetal lung and lung) cells, such as bronchial epithelial cells, lung endothelial cells,[12,34] alveolar epithelial cells (types I and II), and so on.[10,11] In the pulmonary endothelial cells, *PIEZO1* was related to angiogenesis, hydrostatic pressure-induced pulmonary edema, and ventilator-induced lung injury.[35,36] In the lung myeloid cells, *PIEZO1* promoted *HIF-1α* stabilization to trigger inflammation under stress.[13] In alveolar epithelial cells, mechanical stress during the respiratory cycle activated *PIEZO1*, consequently causing a Ca^{2+} influx, thereby releasing an alveolar surfactant.[37] However, there has been no research to prove that the *PIEZO1* protein in the alveolar epithelial cells could regulate RIPI.

PIEZO1 with RIPI

Radiation-induced lung injury includes acute radiation-induced pneumonia and chronic pulmonary fibrosis.[5] In the process of pulmonary injury caused by ionizing radiation, the structure and composition of the extracellular matrix would be damaged, thus leading to high levels of stress and strain throughout the lung.[14] *PIEZO1* could be activated due to changes in the mechanics of the cellular microenvironment.[13] Our ongoing study using the rat type II alveolar epithelial cells (RLE-6TN) found that a single dose of 4-Gy radiation after 8 h increased both the mRNA and protein levels of *PEIZO1* (Fig. 1g, h). The previous study demonstrated that *PIEZO1* induced the *EDN1* expression through the Ca^{2+} influx to drive the *HIF-1α* accumulation and inflammation in the lung myeloid cells.[13] Simultaneously, *HIF-1α* signaling was found to play an essential role in RIPI.[5] During RIPI, the type II alveolar epithe-

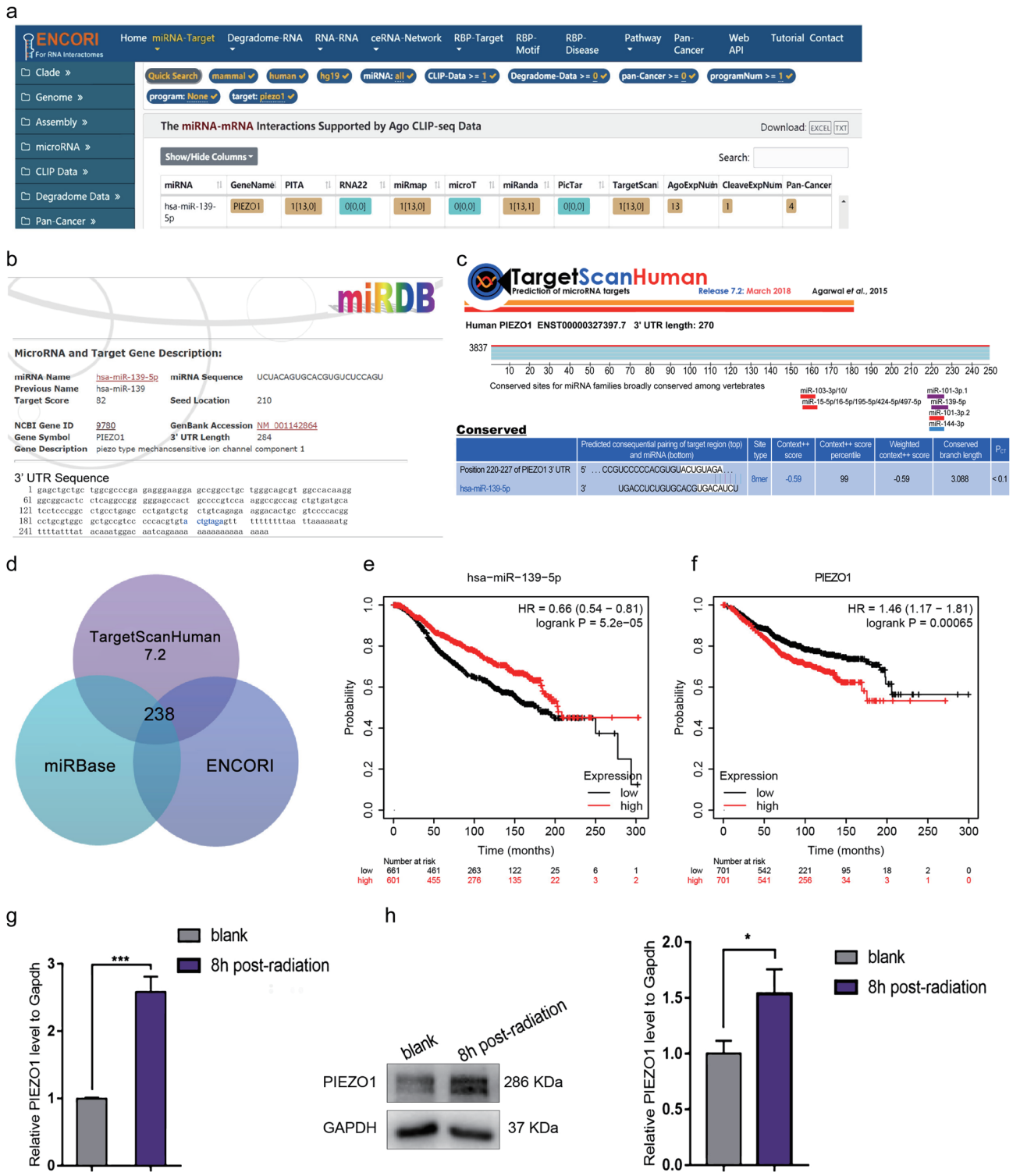

Fig. 1. *PIEZO1* could be a target gene of miR-139-5p, and ionizing radiation would lead to increased *PIEZO1* mRNA and protein expression *in vitro*. A-C, The TargetScanHuman 7.2, miRbase, and ENCORI databases predicted that *PIEZO1* was a target gene of miR-139-5p. D, 238 genes were intersected in three databases predictions. E and F, Kaplan-Meier Plotter[31,32] showed that among breast cancer patients, high miR-139-5p expression and low *PIEZO1* expression were associated with longer survival time. The inverse effects of miR-139-5p and *PIEZO1* on cancer prognosis were consistent with the prediction that *PIEZO1* acted as a target of miR-139-5p. G, The expression of *PIEZO1* mRNA in the RLE-6TN cells was increased at 8 h after radiation (4-Gy). N = 3 per group per time point. H, Representative Western blot images showing that the *PIEZO1* protein expression was increased at 8 h after radiation. (The bars represent SD. The significance was calculated with the Student's *t*-test. *$p < 0.05$ and ***$p < 0.001$). RLE-6TN, rat type II alveolar epithelial cells; SD, Standard deviation.

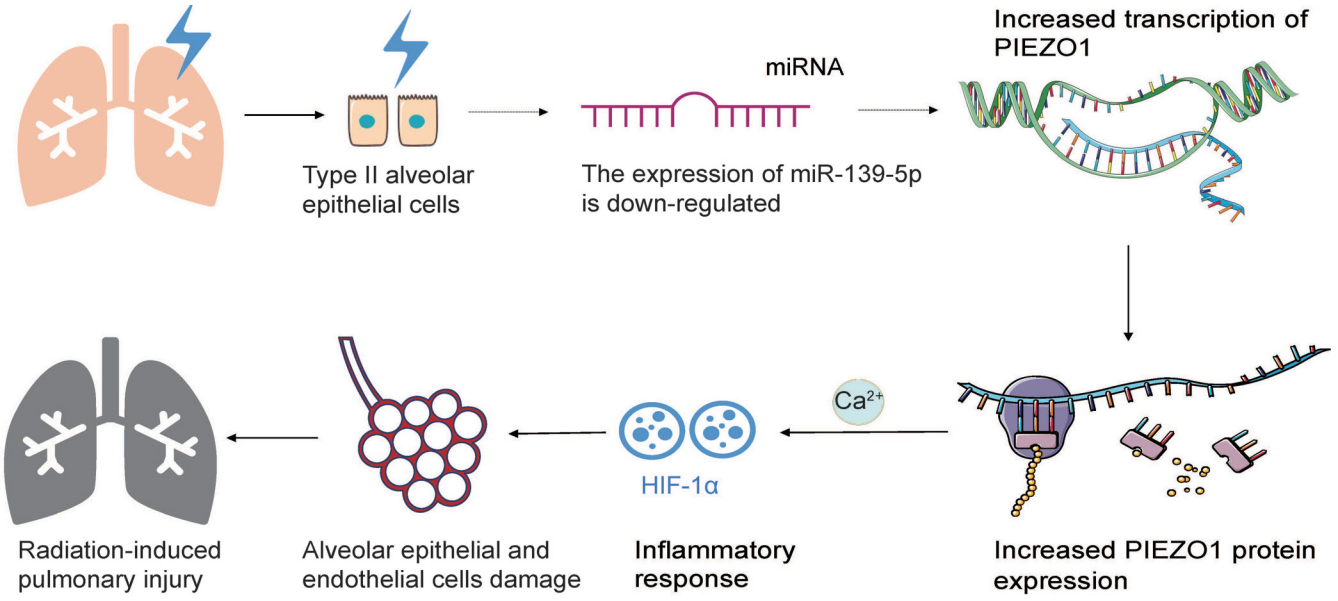

Fig. 2. A schematic plot illustrating the potential role of miR-139-5p/*PIEZO1* signaling in RIPI. When the alveolar type II epithelial cells were subjected to ionizing radiation, the expression of miR-139-5p was inhibited, thus leading to an increased *PIEZO1* expression. The enhanced *PIEZO1* expression could stabilize *HIF-1α*, thereby activating inflammation, damaging the type II epithelial cells as well as endothelial cells, and aggravating RIPI. RIPI, Radiation-induced pulmonary injury.

lial cells could also act as a source of inflammation.[3] Therefore, we further speculated that *PIEZO1* could aggravate lung inflammation after radiation by regulating the *HIF-1α* signaling in type II alveolar epithelial cells.

Verification of the hypothesis and clinical implications

We proposed a novel mechanism whereby miR-139-5p would regulate *PIEZO1*/*HIF-1α* signaling to modulate ionizing radiation-induced pulmonary injury. *PIEZO1* in type II alveolar epithelial cells could act as a potential target in protecting the lung from ionizing radiation injury. This hypothesis would be verified by a series of experiments. Firstly, we would confirm that the decreased expression of miR-139-5p would be accompanied with an increased *PIEZO1* expression after ionizing radiation. Secondly, the miRNA/target gene relationship between miR-139-5p and *PIEZO1* would be validated by a series of experiments. Thirdly, the roles of miR-139-5p and *PIEZO1* in inflammation activated by the type II alveolar epithelial cells after radiation will be examined. Finally, an investigation would be undertaken to examine whether the impact of miR-139-5p on RIPI was dependent on *PIEZO1*/*HIF-1α* signaling.

Future directions

We further tend to conduct a study to confirm whether *PIEZO1* could be modulated by miR-139-5p and would explore the specific mechanisms through molecular biology experiments.

Conclusions

Ionizing radiation inhibits miR-139-5p expression. *PIEZO1* is a predicted downstream target of miR-139-5p. After radiation, the upregulation of the *PIEZO1* expression could aggravate inflammation and promote the development of RIPI in type II alveolar epithelial cells. Therefore, well-designed experiments would be needed to verify this hypothesis.

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Conflict of interest

All authors have no interests to declare.

Author contributions

JH and YL collected the data and wrote the manuscript. XG and XL performed all the bioinformatic analyses. YL offered conceptual insight. YL and HZ suggested intellectual support and supervised the project, and SW helped interpret the work. HZ, XL, and SW participated in the design of the study.

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